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 NEWS  1           Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2           "Ask CAS" for self-help around the clock
 NEWS  3  May 12   EXTEND option available in structure searching
 NEWS  4  May 12   Polymer links for the POLYLINK command completed in REGISTRY
 NEWS  5  May 27   New UPM (Update Code Maximum) field for more efficient patent
                   SDIs in CAplus
 NEWS  6  May 27   CAplus super roles and document types searchable in REGISTRY
 NEWS  7  Jun 22   STN Patent Forums to be held July 19-22, 2004
 NEWS  8  Jun 28   Additional enzyme-catalyzed reactions added to CASREACT
 NEWS  9  Jun 28   ANTE, AQUALINE, BIOENG, CIVILENG, ENVIROENG, MECHENG,
                   and WATER from CSA now available on STN(R)
 NEWS 10  Jul 12   BEILSTEIN enhanced with new display and select options,
                   resulting in a closer connection to BABS

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
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=> FIL CAPLUS
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                      ENTRY    SESSION
FULL ESTIMATED COST                                    0.42       0.42

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FILE COVERS 1907 - 23 Jul 2004 VOL 141 ISS 5
FILE LAST UPDATED: 22 Jul 2004 (20040722/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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=> E "391612-50-3"/BI,RN 25
E1            1      391612-49-0/BI
E2            1      391612-49-0P/BI
E3            1 --> 391612-50-3/BI
E4            0      391612-50-3/RN
E5            1      391612-50-3P/BI
E6            1      391612-51-4/BI
E7            1      391612-51-4P/BI
E8            1      391612-52-5/BI
E9            1      391612-52-5P/BI
E10           1      391612-53-6/BI
E11           1      391612-54-7/BI
E12           1      391612-55-8/BI
E13           1      391612-56-9/BI
E14           1      391612-57-0/BI
E15           1      391612-58-1/BI
E16           1      391612-59-2/BI
E17           1      391612-60-5/BI
E18           1      391612-61-6/BI
E19           1      391612-62-7/BI
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E22           1      391612-64-9P/BI
E23           1      391612-65-0/BI
E24           1      391612-65-0P/BI
E25           4      391612-66-1/BI

=> S E3
L1            1 391612-50-3/BI
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elected species

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=> DIS L1 1 IALL
THE ESTIMATED COST FOR THIS REQUEST IS 3.00 U.S. DOLLARS
DO YOU WANT TO CONTINUE WITH THIS REQUEST? (Y)/N:Y

L1   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2002:72705  CAPLUS
DOCUMENT NUMBER:          136:123688
ENTRY DATE:               Entered STN:  27 Jan 2002
TITLE:                    Preparation of biodegradable high molecular weight
                          polymeric linkers and their drug conjugates
INVENTOR(S):              Greenwald, Richard B.; Zhao, Hong
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S.
                          6,251,382.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
```

current application

LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K031-785
SECONDARY: C08G063-91
US PATENT CLASSIF.: 424078180
CLASSIFICATION: 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 26, 34, 37
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002009426	A1	20020124	US 2001-888072	20010622
US 6251382	B1	20010626	US 1999-293557	19990415

PRIORITY APPLN. INFO.: US 1998-82105P P 19980417
US 1999-293557 A2 19990415
OTHER SOURCE(S): MARPAT 136:123688
ABSTRACT:
The present invention includes polymeric transport systems such as prodrugs of polyoxyethylene with pharmaceuticals such as daunorubicin, and camptothecin. A solution of of m-PEG acid, diaminopimelic aspartic acid camptothecin TFA salt, a 50% solution of 1-propanephosphonic acid cyclic anhydride in EtOAc and N-dimethylaminopyridine in dry dichloromethane was stirred at room temperature overnight followed by washing with 1% aqueous NaHCO3 and 0.1N HCl solution The solvent was removed , and the residue was crystallized from 2-propanol to yield the product.

SUPPL. TERM: polymer prodrug conjugate prepn; anticancer polymer prodrug prepn; polyoxyethylene prodrug anticancer prepn
INDEX TERM: Antitumor agents
(preparation of biodegradable high mol. weight polymeric linkers
and their drug conjugates)
INDEX TERM: Drug delivery systems
(prodrugs; preparation of biodegradable high mol. weight polymeric linkers and their drug conjugates)
INDEX TERM: 96-53-7, 2-Thiazolidinethione 583-93-7 1791-13-5 6057-90-5 7689-03-4 13726-67-5 23541-50-6 24424-99-5 67665-18-3 204133-37-9 391612-43-4
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(preparation of biodegradable high mol. weight polymeric linkers
and their drug conjugates)
INDEX TERM: 98469-29-5P 247920-06-5P 345967-44-4P 345967-45-5P 345967-47-7P 345967-49-9P 345967-51-3P 391612-44-5P 391612-45-6P 391612-46-7P 391612-47-8P 391612-48-9P 391612-49-0P 391669-40-2P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of biodegradable high mol. weight polymeric linkers
and their drug conjugates)
INDEX TERM: **391612-50-3P** 391612-51-4P 391612-52-5P 391669-39-9P
ROLE: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of biodegradable high mol. weight polymeric linkers
and their drug conjugates)
INDEX TERM: 147-94-4D, Cytosine arabinoside, prodrugs 148-82-3D, Melphalan, prodrugs 2067-58-5D, prodrugs 20830-81-3D, prodrugs 23214-92-8D, Doxorubicin, prodrugs 95058-81-4D, Gemcitabine, prodrugs

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                    ROLE: THU (Therapeutic use); BIOL (Biological study); USES
                    (Uses)
                       (preparation of biodegradable high mol. weight polymeric
linkers
                       and their drug conjugates)


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     (FILE 'HOME' ENTERED AT 09:09:04 ON 23 JUL 2004)

     FILE 'CAPLUS' ENTERED AT 09:10:15 ON 23 JUL 2004
               E "391612-50-3"/BI,RN 25
L1             1 S E3

=> index bioscience
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         7.21       7.63

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                        -0.74      -0.74

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS,
       BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT,
       CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DISSABS, DDFB, DDFU,
       DGENE, DRUGB, DRUGMONOG2, ...' ENTERED AT 09:13:17 ON 23 JUL 2004

70 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
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=> s L1
          1   FILE CAPLUS
  38 FILES SEARCHED...
          1   FILE TOXCENTER

   2 FILES HAVE ONE OR MORE ANSWERS,   70 FILES SEARCHED IN STNINDEX

L2   QUE L1

=> d rank
F1             1   CAPLUS
F2             1   TOXCENTER


=> file f1, f2
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         1.14       8.77

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00      -0.74

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=> s l1
L3 2 L1

=> d l3 ibib ti abs ind 1-2

L3 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:72705 CAPLUS
DOCUMENT NUMBER: 136:123688
TITLE: Preparation of biodegradable high molecular weight polymeric linkers and their drug conjugates
INVENTOR(S): Greenwald, Richard B.; Zhao, Hong
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. 6,251,382.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002009426	A1	20020124	US 2001-888072	20010622
US 6251382	B1	20010626	US 1999-293557	19990415

PRIORITY APPLN. INFO.: US 1998-82105P P 19980417
US 1999-293557 A2 19990415
OTHER SOURCE(S): MARPAT 136:123688
TI Preparation of biodegradable high molecular weight polymeric linkers and their drug conjugates
AB The present invention includes polymeric transport systems such as prodrugs of polyoxyethylene with pharmaceuticals such as daunorubicin, and camptothecin. A solution of of m-PEG acid, diaminopimelic aspartic acid camptothecin TFA salt, a 50% solution of 1-propanephosphonic acid cyclic anhydride in EtOAc and N-dimethylaminopyridine in dry dichloromethane was stirred at room temperature overnight followed by washing with 1% aqueous NaHCO3 and 0.1N HCl solution The solvent was removed , and the residue was crystallized from 2-propanol to yield the product.
IC ICM A61K031-785
ICS C08G063-91
NCL 424078180
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 26, 34, 37
ST polymer prodrug conjugate prepn; anticancer polymer prodrug prepn; polyoxyethylene prodrug anticancer prepn
IT Antitumor agents
(preparation of biodegradable high mol. weight polymeric linkers and their drug conjugates)
IT Drug delivery systems
(prodrugs; preparation of biodegradable high mol. weight polymeric linkers and their drug conjugates)
IT 96-53-7, 2-Thiazolidinethione 583-93-7 1791-13-5 6057-90-5 7689-03-4 13726-67-5 23541-50-6 24424-99-5 67665-18-3 204133-37-9 391612-43-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of biodegradable high mol. weight polymeric linkers and their drug

conjugates)
IT 98469-29-5P 247920-06-5P 345967-44-4P 345967-45-5P 345967-47-7P
345967-49-9P 345967-51-3P 391612-44-5P 391612-45-6P 391612-46-7P
391612-47-8P 391612-48-9P 391612-49-0P 391669-40-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of biodegradable high mol. weight polymeric linkers and their drug
conjugates)
IT **391612-50-3P** 391612-51-4P 391612-52-5P 391669-39-9P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of biodegradable high mol. weight polymeric linkers and their drug
conjugates)
IT 147-94-4D, Cytosine arabinoside, prodrugs 148-82-3D, Melphalan, prodrugs 2067-58-5D, prodrugs 20830-81-3D, prodrugs 23214-92-8D, Doxorubicin, prodrugs 95058-81-4D, Gemcitabine, prodrugs
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of biodegradable high mol. weight polymeric linkers and their drug
conjugates)

L3 ANSWER 2 OF 2 TOXCENTER COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:41534 TOXCENTER
COPYRIGHT: Copyright 2004 ACS
DOCUMENT NUMBER: CA136081236880
TITLE: Preparation of biodegradable high molecular weight polymeric linkers and their drug conjugates
AUTHOR(S): Greenwald, Richard B.; Zhao, Hong
PATENT INFORMATION: US 2002009426 A1 24 Jan 2002
SOURCE: (2002) U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. 6,251,382.
CODEN: USXXCO.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2002:72705
LANGUAGE: English
ENTRY DATE: Entered STN: 20020212
Last Updated on STN: 20031117
TI Preparation of biodegradable high molecular weight polymeric linkers and their drug conjugates
AB The present invention includes polymeric transport systems such as prodrugs of polyoxyethylene with pharmaceuticals such as daunorubicin, and camptothecin. A solution of of m-PEG acid, diaminopimelic aspartic acid camptothecin TFA salt, a 50% solution of 1-propanephosphonic acid cyclic anhydride in EtOAc and N-dimethylaminopyridine in dry dichloromethane was stirred at room temperature overnight followed by washing with 1% aqueous NaHCO3
and 0.1N HCl solution The solvent was removed , and the residue was crystallized
from 2-propanol to yield the product.
CC 63-6
ST Miscellaneous Descriptors
polymer prodrug conjugate prepn; anticancer polymer prodrug prepn; polyoxyethylene prodrug anticancer prepn
RN 96-53-7 (2-Thiazolidinethione)
147-94-4Q (Cytosine arabinoside, prodrugs)
148-82-3Q (Melphalan, prodrugs)
2067-58-5Q (prodrugs)
20830-81-3Q (prodrugs)
23214-92-8Q (Doxorubicin, prodrugs)

```
     95058-81-4Q (Gemcitabine, prodrugs)
RN   583-93-7; 1791-13-5; 6057-90-5; 7689-03-4; 13726-67-5; 23541-50-6;
     24424-99-5; 67665-18-3; 204133-37-9; 391612-43-4; 98469-29-5; 247920-06-5;
     345967-44-4; 345967-45-5; 345967-47-7; 345967-49-9; 345967-51-3,
     391612-44-5; 391612-45-6; 391612-46-7; 391612-47-8; 391612-48-9;
     391612-49-0; 391669-40-2; 391612-50-3; 391612-51-4; 391612-52-5;
     391669-39-9


=> d his

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     FILE 'CAPLUS' ENTERED AT 09:10:15 ON 23 JUL 2004
               E "391612-50-3"/BI,RN 25
L1           1 S E3

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DISSABS,
     DDFB, DDFU, DGENE, DRUGB, DRUGMONOG2, ...' ENTERED AT 09:13:17 ON 23 JUL
     2004
               SEA L1
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              1   FILE CAPLUS
              1   FILE TOXCENTER
L2             QUE L1
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     FILE 'CAPLUS, TOXCENTER' ENTERED AT 09:14:17 ON 23 JUL 2004
L3           2 S L1

=> file caplus biosis medline
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       8.18      16.95

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                      -0.74      -1.48

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FILE 'MEDLINE' ENTERED AT 09:15:57 ON 23 JUL 2004

=> s polymer? link? and biodegrad?
L4           19 POLYMER? LINK? AND BIODEGRAD?

=> s L4 and (greenwald,r? OR zhao,h?)/AU
L5            3 L4 AND (GREENWALD,R? OR ZHAO,H?)/AU

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6            2 DUP REM L5 (1 DUPLICATE REMOVED)

=> d l6 ibib ti abs
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L6 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:72705 CAPLUS
DOCUMENT NUMBER: 136:123688
TITLE: Preparation of **biodegradable** high molecular weight **polymeric linkers** and their drug conjugates
INVENTOR(S): **Greenwald, Richard B.; Zhao, Hong**
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 39 pp., Cont.-in-part of U.S. 6,251,382.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002009426	A1	20020124	US 2001-888072	20010622
US 6251382	B1	20010626	US 1999-293557	19990415

PRIORITY APPLN. INFO.: US 1998-82105P P 19980417
US 1999-293557 A2 19990415
OTHER SOURCE(S): MARPAT 136:123688
TI Preparation of **biodegradable** high molecular weight **polymeric linkers** and their drug conjugates
AB The present invention includes polymeric transport systems such as prodrugs of polyoxyethylene with pharmaceuticals such as daunorubicin, and camptothecin. A solution of of m-PEG acid, diaminopimelic aspartic acid camptothecin TFA salt, a 50% solution of 1-propanephosphonic acid cyclic anhydride in EtOAc and N-dimethylaminopyridine in dry dichloromethane was stirred at room temperature overnight followed by washing with 1% aqueous NaHCO3 and 0.1N HCl solution The solvent was removed , and the residue was crystallized from 2-propanol to yield the product.

=> d l6 ibib ti abs 2

L6 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2001:468173 CAPLUS
DOCUMENT NUMBER: 135:66230
TITLE: **Biodegradable** high molecular weight **polymeric linkers** and their conjugates
INVENTOR(S): **Greenwald, Richard B.**; Martinez, Anthony J.; Choe, Yun H.; Pendri, Annapurna
PATENT ASSIGNEE(S): Enzon, Inc., USA
SOURCE: U.S., 32 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6251382	B1	20010626	US 1999-293557	19990415
US 2002009426	A1	20020124	US 2001-888072	20010622

PRIORITY APPLN. INFO.: US 1998-82105P P 19980417
US 1999-293557 A2 19990415
OTHER SOURCE(S): MARPAT 135:66230
TI **Biodegradable** high molecular weight **polymeric**

linkers and their conjugates

AB Methods of preparing polymer conjugates of a biol. active compound having an available hydroxy (or amine) group which undergoes a substitution reaction, as prodrugs, and methods of treatment using the same are described. A biol. active compound is a member of the group consisting of antitumor, cardiovascular, anti-infective, antifungal, antianxiety, gastrointestinal, central nervous system-activating, analgesic, fertility or contraceptive, anti-inflammatory, steroidal, anti-uremic, vasodilating and vasoconstricting agents, and a polymer is a polyalkylene oxide, e.g., polyethylene oxide. For example, mPEG was conjugated with diaminopimelic aspartic camptothecin or with diaminopimelic camptothecin to yield 0.8 g (80% yield) and 1.85 g (93% yield) of products, resp.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d his

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FILE 'CAPLUS' ENTERED AT 09:10:15 ON 23 JUL 2004
E "391612-50-3"/BI,RN 25
L1 1 S E3

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DISSABS, DDFB, DDFU, DGENE, DRUGB, DRUGMONOG2, ...' ENTERED AT 09:13:17 ON 23 JUL 2004

	SEA L1
1	FILE CAPLUS
1	FILE TOXCENTER

L2 QUE L1

FILE 'CAPLUS, TOXCENTER' ENTERED AT 09:14:17 ON 23 JUL 2004
L3 2 S L1

FILE 'CAPLUS, BIOSIS, MEDLINE' ENTERED AT 09:15:57 ON 23 JUL 2004
L4 19 S POLYMER? LINK? AND BIODEGRAD?
L5 3 S L4 AND (GREENWALD,R? OR ZHAO,H?)/AU
L6 2 DUP REM L5 (1 DUPLICATE REMOVED)

=> s l4 not l5
L7 16 L4 NOT L5

=> d l7 ibib ti abs ind 1-16

L7 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:270099 CAPLUS
DOCUMENT NUMBER: 140:292657
TITLE: **Polymer-linker**-drug conjugates for targeted drug delivery
INVENTOR(S): Chau, Ying; Langer, Robert S.
PATENT ASSIGNEE(S): Massachusetts Institute of Technology, USA
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004027045	A2	20040401	WO 2003-US29898	20030923
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004116348	A1	20040617	US 2003-668045	20030922

PRIORITY APPLN. INFO.: US 2002-412760P P 20020923
US 2003-668045 A 20030922

TI **Polymer-linker**-drug conjugates for targeted drug delivery

AB A system for selectively delivering drugs to target tissues is provided. The system includes a **polymer-linker**-drug conjugate. The linker includes a segment that is recognized and cleaved by a digestive enzyme that is overexpressed in the extracellular space of the target tissue. The recognition segment is preferably an oligopeptide or oligosaccharide segment. The polymeric carrier is preferably hydrophilic, **biodegradable** and biocompatible particle. Any drug may be delivered using a conjugate prepared according to the invention. CM-dextran-oligopeptide-doxorubicin conjugates were prepared and cytotoxic activity determined Peptidyldoxorubicin release in the presence of MMP-2 was also determined

IC ICM C12N

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 33, 34

ST antitumor drug conjugate peptide dextran delivery

IT Polyoxyalkylenes, biological studies
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates with dextran and peptides and doxorubicin; **polymer-linker**-drug conjugates for targeted drug delivery)

IT Peptides, biological studies
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates, with dextrans and antitumor agents; **polymer-linker**-drug conjugates for targeted drug delivery)

IT Antitumor agents
Drug delivery systems
(**polymer-linker**-drug conjugates for targeted drug delivery)

IT 146480-35-5, MMP 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**polymer-linker**-drug conjugates for targeted drug delivery)

IT 59-05-2DP, Methotrexate, conjugates with and peptides and dextran 929-59-9DP, conjugates with peptides and methotrexate 9004-74-4DP, Methoxypolyethylene glycol, conjugates with and peptides and doxorubicin 9044-05-7DP, Carboxymethyl dextran, conjugates with peptides and doxorubicin 23214-92-8DP, Doxorubicin, conjugates with dextrans and peptides 25322-68-3DP, Peg, conjugates with dextran and peptides and doxorubicin 676227-19-3DP, conjugates with dextrans and doxorubicin 676227-20-6DP, conjugates with dextrans and doxorubicin 676227-21-7DP, conjugates with dextrans and doxorubicin 676227-22-8DP, conjugates with

dextrans and doxorubicin 676227-23-9DP, conjugates with dextrans and doxorubicin
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**polymer-linker**-drug conjugates for targeted drug delivery)

IT 9004-54-0, Dextran, reactions 19741-14-1, 4-Amino-4-deoxy-N10-methylpteroic acid 45120-30-7, L-Glutamic acid α-tert-butyl ester
RL: RCT (Reactant); RACT (Reactant or reagent)
(**polymer-linker**-drug conjugates for targeted drug delivery)

IT 9044-05-7P, Carboxymethyl dextran 79640-70-3P, Methotrexate α-tert-butyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**polymer-linker**-drug conjugates for targeted drug delivery)

L7 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:678871 CAPLUS
DOCUMENT NUMBER: 139:214915
TITLE: Hydrolytically-degradable alkylene oxide polymers, preparation, hydrogels, and biological conjugate delivery system
INVENTOR(S): Bentley, Michael D.; Harris, J. Milton; Zhao, Xuan; Battle, William Dudle, III
PATENT ASSIGNEE(S): Nektar Therapeutics Al, Corporation, USA
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003070805	A1	20030828	WO 2003-US5113	20030214

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-357350P P 20020215

TI Hydrolytically-degradable alkylene oxide polymers, preparation, hydrogels, and biological conjugate delivery system

AB A water-soluble, nonpeptidic polymer comprises ≥2 alkylene oxide-based oligomers linked together by hydrolytically degradable linkages such as carbonates. Typically, the oligomer portion of the polymer is an amphiphilic triblock copolymer having a central propylene oxide block or butylene oxide block positioned between 2 ethylene oxide blocks. The polymer can be hydrolytically degraded into oligomers under physiol. conditions. In aqueous media, the polymer preferably forms thermally-reversible, hydrolytically-degradable hydrogels that can be used for PEGylated drug delivery and related biomedical applications.

IC ICM C08G065-00
ICS C08G064-18; A61K009-20; A61K009-70

CC 35-5 (Chemistry of Synthetic High Polymers)
ST polyoxyalkylene carbonate hydrogel hydrolytic degrdn
IT Polyoxyalkylenes, preparation
RL: IMF (Industrial manufacture); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(block; hydrolytically-degradable alkylene oxide **polymers** **linked** through carbonate groups)
IT Drug delivery systems
(carriers; hydrolytically-degradable alkylene oxide **polymers** **linked** through carbonate groups)
IT Antibodies and Immunoglobulins
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugate with hydrolytically-degradable alkylene oxide block copolymer; hydrolytically-degradable alkylene oxide **polymers** **linked** through carbonate groups)
IT Hydrogels
(hydrolytically-degradable alkylene oxide **polymers** **linked** through)
IT **Biodegradable** materials
(hydrolytically-degradable alkylene oxide **polymers** **linked** through carbonate groups)
IT 32315-10-9, Triphosgene
RL: RCT (Reactant); RACT (Reactant or reagent)
(coupling agent; hydrolytically-degradable alkylene oxide **polymers** **linked** through)
IT 587023-77-6P
RL: IMF (Industrial manufacture); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrolytically-degradable alkylene oxide **polymers** **linked** through carbonate groups)
IT 251636-65-4P, Ethylene oxide-propylene oxide block copolymer mesylate
RL: IMF (Industrial manufacture); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(hydrolytically-degradable alkylene oxide **polymers** **linked** through carbonate groups)
IT 60842-46-8DP, FITC-dextran, conjugate with hydrolytically-degradable alkylene oxide block copolymer 83916-01-2DP, Biphalin, conjugate with hydrolytically-degradable alkylene oxide block copolymer 587023-77-6DP, conjugate with biol. active mol.
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydrolytically-degradable alkylene oxide **polymers** **linked** through carbonate groups)
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:558232 CAPLUS
DOCUMENT NUMBER: 140:133744
TITLE: Development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application
AUTHOR(S): Sen Gupta, A.; Lopina, S. T.
CORPORATE SOURCE: Department of Chemical Engineering, The University of Akron, Akron, OH, 44325, USA
SOURCE: Materials Science Forum (2003), 426-432(Pt. 4, THERMEC'2003), 3261-3266
CODEN: MSFOEP; ISSN: 0255-5476
PUBLISHER: Trans Tech Publications Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Development of novel "pseudo"polypeptidic **biodegradable** polymers

based on natural amino acid L-tyrosine for biomaterial application

AB Synthetic **biodegradable** polymers, using natural metabolites as monomers, have been established as an effective class of biomaterials. The **biodegrdn.** of such polymers into the corresponding naturally metabolizable monomers and their derivs. renders the polymers biocompatible. Amino acid "monomers" seem a logical choice for the development of such biomaterials. Despite their biocompatibility, use of poly(amino acids) is limited by practical difficulties like insoly. in common organic solvents, thermolability, unpredictable water intake and swelling behavior, etc., which have been traced back to the highly crystalline structure and hydrogen bonding induced by the sequence of amide(peptide) bonds in the polymer backbone. Hence introduction of non-amide bonds alternating with the amide(peptide) link in the poly(amino acid) backbone is being investigated as one of the ways to circumvent such properties. The resulting polymer would be called a "pseudo"poly(amino acid). The non-peptide link is expected to impart properties that are potentially favorable for biomaterial applications. In this paper development of such "pseudo"poly(amino acids) starting from natural amino acid L-tyrosine, is described. The process involves the synthesis of a model diphenolic compound containing a peptide link, from L-tyrosine. This compound is further polymerized through the phenolic terminals using conventional tools of polymer chemical to produce non-peptidic **polymeric linkages**. The resulting polymers, namely, a polycarbonate and a polyphosphate are characterized for their physicochem. properties. Based upon preliminary investigation of these properties, potential biomaterial applications of such polymers are discussed.

CC 63-7 (Pharmaceuticals)
Section cross-reference(s): 35

ST tyrosine deriv polymer biomaterial; biomaterial pseudo polyamino acid

IT Medical goods
(**biodegradable**; development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application)

IT Polymer degradation
(biol.; development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application)

IT Glass transition temperature
Prosthetic materials and Prosthetics
(development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application)

IT Polycarbonates, biological studies
Polyphosphates
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application)

IT **Biodegradable** materials
(medical; development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application)

IT Polyamides, biological studies
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(poly(amino acids); development of novel "pseudo"polypeptidic **biodegradable** polymers based on natural amino acid L-tyrosine for biomaterial application)

IT 214957-41-2P 573691-00-6P
RL: PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(development of novel "pseudo"polypeptidic **biodegradable**

polymers based on natural amino acid L-tyrosine for biomaterial application)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:708929 CAPLUS
DOCUMENT NUMBER: 129:339862
TITLE: Diamido-diamine polymer-platinum compounds for tumor treatment, and preparation thereof
INVENTOR(S): Duncan, Ruth; Ferruti, Paolo; Evagorou, Evagoras G.
PATENT ASSIGNEE(S): Access Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9847496	A2	19981029	WO 1998-US7659	19980415
WO 9847496	A3	19990211		
W: AU, CA, JP, MX, TR				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9871245	A1	19981113	AU 1998-71245	19980415
US 5985916	A	19991116	US 1998-62372	19980417

PRIORITY APPLN. INFO.: US 1997-44701P P 19970418
WO 1998-US7659 W 19980415

TI Diamido-diamine polymer-platinum compounds for tumor treatment, and preparation thereof
AB A polymer-platinum compound for use in tumor treatment is described. The compound is composed of a **biodegradable** diamido-diamine **polymer linked** to a platinum species. The platinum species is released from the polymer to yield a platinum species having anti-tumor activity.
IC ICM A61K031-00
CC 1-6 (Pharmacology)
Section cross-reference(s): 35, 63
ST antitumor diamidodiamine polymer platinum compd prepn
IT Antitumor agents
Drug delivery systems
Drug targeting
(diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)
IT Drug delivery systems
(parenterals; diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)
IT Polyamines
Polyamines
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamide-, reaction products, with platinum compds.; diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)
IT Polyamides, biological studies
Polyamides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyamine-, reaction products, with platinum compds.; diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)

IT Oligosaccharides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polycyclic, polymer reaction products, platinum species-linked; diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)

IT 15663-27-1, Cisplatin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)

IT 15663-27-1DP, Cisplatin, polymer reaction products 215312-73-5DP, cisplatin reaction products 215382-15-3DP, cisplatin reaction products 215382-18-6DP, cisplatin reaction products
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)

IT 7440-06-4D, Platinum, compds., polymer reaction products, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)

IT 215312-73-5P 215382-15-3P 215382-18-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction; diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)

IT 7440-06-4, Platinum, processes
RL: PEP (Physical, engineering or chemical process); PROC (Process)
(release; diamido-diamine polymer-platinum compds. for tumor treatment, and preparation thereof)

L7 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1991:663330 CAPLUS
DOCUMENT NUMBER: 115:263330
TITLE: Biodistribution of trans-1,2-diaminocyclohexane-trimellitatoplatinum(II) attached to macromolecular carriers. I. Poly(hydroxyethyl-D,L-asparagine) carrier
AUTHOR(S): Filipova-Voprsalova, Marie; Drobnik, Jaroslav; Sramek, Blahoslav; Kvetina, Jaroslav
CORPORATE SOURCE: Inst. Exp. Biopharm., Hradec Kralove, Czech.
SOURCE: Journal of Controlled Release (1991), 17(1), 89-97
CODEN: JCREEC; ISSN: 0168-3659
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Biodistribution of trans-1,2-diaminocyclohexane-trimellitatoplatinum(II) attached to macromolecular carriers. I. Poly(hydroxyethyl-D,L-asparagine) carrier

AB Two types of macromol. drug forms of the second generation platinum antitumor drug 4-carboxyphthalato-(trans-1,2-diaminocyclohexane)platinum(II) (TMA) were prepared with nonbiodegradable carriers derived from racemic poly(N4-substituted aspartamide): AN type was prepared from N-(2-hydroxyethyl) and AR type from N-(2-hydroxypropyl) derivative by acylation with trimellitato residues, thus yielding primary and secondary ester bonds resp. Plasma levels, urinary excretion and organ deposition of platinum were followed after administration into rats. When compared

with free TMA both types of macromol. forms showed a retardation effect in platinum pharmacokinetics with the most pronounced differences using the AR type. Considering all possible **biodegradable** bonds in the polymeric drug forms the nature of the drug-**polymer link** seemed to play an important role in the kinetics of drug release as revealed by the differences between the AN and AR type.

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 34

ST diaminocyclohexane trimellitatoplatinum carrier biodistribution; polyhydroxyethylasparagine carrier platinum complex; antitumor platinum polyhydroxyethylasparagine carrier

IT Kidney, metabolism
Liver, metabolism
Lung, metabolism
Spleen, metabolism
(diaminocyclohexane-trimellitatoplatinum reaction products with poly(hydroxyalkyl)asparagine uptake by)

IT Drug bioavailability
(of diaminocyclohexanetrimellitatoplatinum, from poly(hydroxyalkyl)asparagine carriers)

IT Pharmaceutical dosage forms
(poly(hydroxyalkyl)asparagine carriers in, platinum drugs biodistribution from)

IT 27881-03-4DP, Poly(DL-succinimide), aminolysis products with hydroxylamines, reaction products with diaminocyclohexanetrimellitoplatinum
RL: SPN (Synthetic preparation); PREP (Preparation)
(poly(hydroxyalkyl)aspartamide-containing, preparation and biodistribution of)

IT 108867-35-2DP, reaction products with poly(hydroxyalkyl)aspartamides
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and biodistribution of)

IT 38780-40-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with silver nitrate)

IT 60732-70-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction with trimellitate)

IT 10025-99-7, Dipotassium tetrachloroplatinate
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with diaminocyclohexane dichloride)

IT 1121-22-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with dipotassium tetrachloroplatinate)

L7 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1990:145395 CAPLUS
DOCUMENT NUMBER: 112:145395
TITLE: Anticancer agents coupled to N-(2-hydroxypropyl)methacrylamide copolymers. 3. Evaluation of adriamycin conjugates against mouse leukemia L1210 in vivo
AUTHOR(S): Duncan, Ruth; Hume, Isabella C.; Kopeckova, Pavla; Ulbrich, Karel; Strohalm, Jiri; Kopecek, Jindrich
CORPORATE SOURCE: Dep. Biol. Sci., Univ. Keele, Keele/Staffordshire, ST5 5BG, UK
SOURCE: Journal of Controlled Release (1989), 10(1), 51-63
CODEN: JCREEC; ISSN: 0168-3659
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Anticancer agents coupled to N-(2-hydroxypropyl)methacrylamide copolymers.

3. Evaluation of adriamycin conjugates against mouse leukemia L1210 in vivo

AB N-(2-Hydroxypropyl)methyacrylamide (HPMA) copolymers were synthesized containing adriamycin (ADR) and in certain cases fucosylamine or galactosamine residues. Drug was attached to polymer via **biodegradable** (-Gly-Phe-Leu-Gly) or nonbiodegradable (-Gly-Gly) oligopeptide side-chains. Fucosylamine and galactosamine were included to promote conjugate targeting to L1210 cells and hepatocytes, resp. Although free ADR (5 mg/kg) can increase the mean life span of DBA2 mice bearing L1210 leukemia (up to 24%), animals do not survive beyond this time. Treatment with P-Gly-Phe-Leu-Gly-ADR (5 mg/kg) consistently increased mean survival time, and in addition produced survivors at 50 days (up to 80% surviving). Polymers containing in addition galactosamine or fucosylamine were equally effective. Degradation of the drug-**polymer linkage** was a prerequisite for pharmacol. activity, P-Gly-Gly-ADR was totally ineffective. Conjugation of ADR limited toxicity, a >10 fold increase in dose could be given in the polymer-bound form without obvious ill effect. Measurement of the pharmacokinetics of 125I-labeled HPMA copolymer-ADR conjugates showed a marked alteration from the pattern of distribution reported previously for free ADR, and the levels of radioactivity detected in the heart were extremely low. The latter observation supports the observed decrease in toxicity seen for conjugated drug.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1, 33, 35

ST adriamycin hydroxypropylmethacrylamine conjugate antitumor; leukemia adriamycin hydroxypropylmethacrylamine conjugate

IT Intestine, metabolism
Kidney, metabolism
Liver, metabolism
(adriamycin-hydroxypropylmethacrylamide conjugates distribution in, antileukemic activity in relation to)

IT Pharmaceutical dosage forms
(for adriamycin, soluble polymer carriers for)

IT Neoplasm inhibitors
(leukemia, adriamycin-hydroxypropylmethacrylamide conjugates as)

IT 4985-46-0DP, Tyrosinamide, conjugates with hydroxypropylmethacrylamide-methacryloyl peptide derivative copolymers and adriamycin and amino sugars 7535-00-4DP, Galactosamine, conjugates with adriamycin and hydroxypropylmethacrylamide-methacryloyl peptide derivs. 7577-62-0DP, conjugates with adriamycin and hydroxypropylmethacrylamide-methacryloyl peptide derivs. 25316-40-9DP, Adriamycin, conjugates with hydroxypropylmethacrylamide-methacryloyl peptide derivative copolymers and amino sugars 57950-81-9DP, conjugates with amino sugars and adriamycin 125929-74-0DP, conjugates with amino sugars and adriamycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antileukemic activity of)

L7 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1987:605099 CAPLUS
DOCUMENT NUMBER: 107:205099
TITLE: Coupling of naltrexone to **biodegradable** poly(α-amino acids)
AUTHOR(S): Negishi, Naoki; Bennett, David B.; Cho, Chong Su; Jeong, Seo Young; Van Heeswijk, Wolfgang A. R.; Feijen, Jan; Kim, Sung Wan
CORPORATE SOURCE: Dep. Pharm., Univ. Utah, Salt Lake City, UT, 84112, USA
SOURCE: Pharmaceutical Research (1987), 4(4), 305-10
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English

TI Coupling of naltrexone to **biodegradable** poly(α-amino acids)

AB The narcotic antagonist naltrexone (I) was modified at the 3 and 14 OH positions and covalently coupled to a **biodegradable** poly(α-amino acid) backbone through a labile bond. Selective acetylation of I with acetic anhydride gave I 3-acetate (II), which was subsequently succinoylated to I 3-acetate-14-hemisuccinate (III) with succinic anhydride. The polymeric backbone chosen for initial coupling expts. was poly-N5-(3-hydroxypropyl)-L-glutamine (PHPG). The side-chain OH functionality permitted covalent bonding of III through an ester linkage. Hydrolysis of covalently bound drug to give I or its derivs. (II and III) should be much slower than diffusion of drug through the polymer matrix. While hydrolysis of I from the polymer side chain is first order, the release of drug from the matrix can be zero order due to the geometry of the device and the phys. and chemical interactions between I and the polymer matrix. iN vitro studies of PHPG-I conjugate in disk form did not show constant release because of the hydrophilic nature of the polymer backbone and the changing local chemical environment upon hydrolysis of drug-**polymer linkages**. The conjugated system was made more hydrophobic by coupling drug to copolymers of hydroxypropyl-L-glutamine (HPG) and L-leucine. Conjugates of III coupled with copoly(HPG-70/Leu-30) demonstrated a nearly constant, but slightly declining release rate of I and its derivs. for 28 days in vitro.

CC 63-6 (Pharmaceuticals)

ST naltrexone polyamino acid conjugate; sustained release naltrexone polyamino acid

IT Hydrolysis
Solution rate
(of naltrexone-poly(amino acid) conjugates)

IT Peptides, esters
RL: SPN (Synthetic preparation); PREP (Preparation)
(esters, conjugates with naltrexone, preparation of and naltrexone prolonged release from)

IT Pharmaceutical dosage forms
(sustained-release, for naltrexone, **biodegradable** poly(amino acid) conjugates in)

IT 111129-15-8P, Naltrexone-3-acetate-14-hemisuccinate
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and coupling to poly(amino acids))

IT 111129-14-7P, Naltrexone-3-acetate
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and succinoylation of)

IT 25569-41-9DP, Poly[N5-(3-hydroxypropyl)-L-glutamine], reaction products with naltrexone esters 38439-11-1DP, reaction products with naltrexone esters
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of and naltrexone prolonged release from)

IT 16590-41-3, Naltrexone
RL: BIOL (Biological study)
(prolonged release of, **biodegradable** poly(amino acid) conjugates for)

IT 111129-16-9, Naltrexone-14-hemisuccinate
RL: PROC (Process)
(release of, from naltrexone-poly(amino acid) conjugates)

L7 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1986:74926 CAPLUS
DOCUMENT NUMBER: 104:74926
TITLE: Poly-L-aspartic acid as a carrier for doxorubicin: a comparative in vivo study of free and polymer-bound drug
AUTHOR(S): Pratesi, G.; Savi, G.; Pezzoni, G.; Bellini, O.;

Penco, S.; Tinelli, S.; Zunino, F.
CORPORATE SOURCE: Ist. Naz. Studio Cura Tumori, Milan, Italy
SOURCE: British Journal of Cancer (1985), 52(6), 841-8
CODEN: BJCAAI; ISSN: 0007-0920
DOCUMENT TYPE: Journal
LANGUAGE: English
TI Poly-L-aspartic acid as a carrier for doxorubicin: a comparative in vivo study of free and polymer-bound drug
AB Poly(L-aspartic acid) (I), (mol. weight = 20,000) was used as a macromol. carrier for doxorubicin (II) [23214-92-8]. The drug was released in vivo through hydrolysis of the ester linkage formed between the carboxyl groups of the polymer and the drug side chain. I was a suitable carrier since it is a soluble, **biodegradable**, multivalent and nontoxic polymer. The toxicity and the therapeutic efficacy of free and **polymer-linked** II were evaluated in normal and tumor-bearing mice, using a variety of exptl. tumor systems. In studies on single and multiple drug administration, the polymeric derivative of II had approx. 3-fold lower toxicity than the free drug. The severity of specific toxic effects, including cardio-, and vesicant toxicity, were appreciably reduced following conjugation to I. I-II conjugate gave similar or rather greater therapeutic effects than free drug at less toxic doses. This effect, more evident in the highly sensitive tumors, improves the therapeutic index of the **polymer-linked** drug.
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 1
ST doxorubicin carrier aspartic acid polymer; antitumor carrier aspartic acid polymer
IT Neoplasm inhibitors
(doxorubicin, carriers for, poly(aspartic acid) as)
IT Polyamides, biological studies
RL: BIOL (Biological study)
(poly(amino acids), doxorubicin carrier systems containing, drug release from)
IT 20830-81-3 65026-79-1
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antitumor activity of)
IT 23214-92-8
RL: BIOL (Biological study)
(carrier for, poly(aspartic acid) as)
IT 23214-92-8D, reaction products with poly(aspartic acid) 25608-40-6D, reaction products with doxorubicin 26063-13-8D, reaction products with doxorubicin
RL: BIOL (Biological study)
(carrier systems containing, drug release from)

L7 ANSWER 9 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2000:292073 BIOSIS
DOCUMENT NUMBER: PREV200000292073
TITLE: Polymer-platinum compounds.
AUTHOR(S): Duncan, Ruth [Inventor, Reprint author]; Ferruti, Paolo [Inventor]; Evagorou, Evagoras G. [Inventor]
CORPORATE SOURCE: London, UK
ASSIGNEE: Access Pharmaceuticals, Inc., Dallas, TX, USA
PATENT INFORMATION: US 5985916 November 16, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 16, 1999) Vol. 1228, No. 3. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Jul 2000
Last Updated on STN: 7 Jan 2002
TI Polymer-platinum compounds.

AB A polymer-platinum compound for use in tumor treatment is described. The compound is composed of a **biodegradable** diamido-diamine **polymer linked** to a platinum species. The platinum species is released from the polymer to yield a platinum species having anti-tumor activity.

NCL 514492000

CC General biology - Miscellaneous 00532

IT Major Concepts
Pharmaceuticals (Pharmacology); Tumor Biology

IT Chemicals & Biochemicals
polymer-platinum compound: antineoplastic agent

L7 ANSWER 10 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1992:7368 BIOSIS

DOCUMENT NUMBER: PREV199293007368; BA93:7368

TITLE: BIODISTRIBUTION OF TRANS-1 2 DIAMINOCYCLOHEXANETRIMELLITATO PLATINUM-II ATTACHED TO MACROMOLECULAR CARRIERS I. POLYHYDROXYETHYL-D L-ASPARAGINE CARRIER.

AUTHOR(S): FILIPOVA-VOPRSALOVA M [Reprint author]; DROBNIK J; SRAMEK B; KVETINA J

CORPORATE SOURCE: CHARLES UNIV, FAC PHARMACY, 501 65 HRADEC, KRALOVE, CZECH

SOURCE: Journal of Controlled Release, (1991) Vol. 17, No. 1, pp. 89-98.
CODEN: JCREEC. ISSN: 0168-3659.

DOCUMENT TYPE: Article

FILE SEGMENT: BA

LANGUAGE: ENGLISH

ENTRY DATE: Entered STN: 10 Dec 1991
Last Updated on STN: 10 Dec 1991

TI BIODISTRIBUTION OF TRANS-1 2 DIAMINOCYCLOHEXANETRIMELLITATOPLATINUM-II ATTACHED TO MACROMOLECULAR CARRIERS I. POLYHYDROXYETHYL-D L-ASPARAGINE CARRIER.

AB Two types of macromolecular drug forms of the second generation platinum antitumor drug 4-carboxyphtalato-(trans, 1,2-diaminocyclohexane)platinum (II) (TMA) were prepared with non-**biodegradable** carriers derived from racemic poly (N4-substituted aspartamide): AN type was prepared from N-(2-hydroxyethyl) and AR type from N-(2-hydroxypropyl) derivative by acylation with trimellitato residues, thus yielding primary and secondary ester bonds respectively. Plasma levels, urinary excretion and organ deposition of platinum were followed after administration into rats. When compared with free TMA both types of macromolecular forms showed a retardation effect in platinum pharmacokinetics with the most pronounced differences using the AR type. Considering all possible **biodegradable** bonds in the polymeric drug forms the nature of the drug-**polymer link** seemed to play an important role in the kinetics of drug release as revealed by the differences between the AN and AR type.

CC Biochemistry methods - Proteins, peptides and amino acids 10054
Biochemistry methods - Minerals 10059
Biochemistry studies - Minerals 10069
Biophysics - Molecular properties and macromolecules 10506
Pharmacology - Drug metabolism and metabolic stimulators 22003
Routes of immunization, infection and therapy 22100
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; Tumor Biology

IT Miscellaneous Descriptors
MAMMAL RAT ANTINEOPLASTIC-DRUG CANCER PHARMACEUTICALS PHARMACOKINETICS DRUG DELIVERY

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia

Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

L7 ANSWER 11 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1990:6655 BIOSIS
DOCUMENT NUMBER: PREV199089006655; BA89:6655
TITLE: ANTICANCER AGENTS COUPLED TO N-2 HYDROXYPROPYL-METHACRYLAMIDE COPOLYMERS 3. EVALUATION OF ADRIAMYCIN CONJUGATES AGAINST MOUSE LEUKEMIA L1210 IN-VIVO.
AUTHOR(S): DUNCAN R [Reprint author]; HUME I C; KOPECKOVA P; ULBRICH K; STROHALM J; KOPECEK J
CORPORATE SOURCE: CANCER RES CAMPAIGN LAB, DEP BIOLOGICAL SCI, UNIV KEELE, KEELE, STAFFORDSHIRE ST5 5BG, GREAT BRITAIN, UK
SOURCE: Journal of Controlled Release, (1989) Vol. 10, No. 1, pp. 51-64.
CODEN: JCREEC. ISSN: 0168-3659.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 5 Dec 1989
Last Updated on STN: 1 Feb 1990

TI ANTICANCER AGENTS COUPLED TO N-2 HYDROXYPROPYL-METHACRYLAMIDE COPOLYMERS 3. EVALUATION OF ADRIAMYCIN CONJUGATES AGAINST MOUSE LEUKEMIA L1210 IN-VIVO.

AB N-(2-Hydroxypropyl)methacrylamide (HPMA) copolymers were synthesized to contain adriamycin (ADR) and in certain cases fucosylamine or galactosamine residues. Drug was attached to polymer via **biodegradable** (-Gly-Phe-Leu-Gly) or non-**biodegradable** (-Gly-Gly) oligopeptide side-chains. Fucosylamine and galactosamine were included to promote conjugate targeting to L1210 cells and hepatocytes, respectively. Although free ADR (5 mg/kg) can increase the mean life span of DBA2 mice bearing L1210 leukaemia (up to 24%), animals do not survive beyond this time. Treatment with P-Gly-Phe-Leu-Gly-ADR (5 mg/kg) consistently increased mean survival time, and in addition produced survivors at 50 days (up to 80% surviving). Polymers containing in addition galactosamine or fucosylamine were equally effective. Degradation of the drug-**polymer linkage** was shown to be a prerequisite for pharmacological activity, P-Gly-Gly-ADR was totally ineffective. Conjugation of ADR limited toxicity, a > 10 fold increase in dose could be given in the polymer-bound form without obvious ill effect. Measurement of the pharmacokinetics of 125I-labelled HPMA copolymer-ADR conjugates showed a marked alteration from the pattern of distribution reported previously for free ADR, and the levels of radioactivity detected in the heart were extremely low. The latter observation supports the observed decrease in toxicity seen for conjugated drug.

CC Cytology - Animal 02506
Radiation biology - Radiation and isotope techniques 06504
Biochemistry studies - General 10060
Biochemistry studies - Nucleic acids, purines and pyrimidines 10062
Pathology - Therapy 12512
Cardiovascular system - Heart pathology 14506
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Pharmacology - Drug metabolism and metabolic stimulators 22003
Routes of immunization, infection and therapy 22100
Toxicology - Pharmacology 22504
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cardiovascular System (Transport and Circulation); Pharmacology; Toxicology; Tumor Biology

IT Miscellaneous Descriptors

MOUSE ANTINEOPLASTIC-DRUG PHARMACEUTICALS PHARMACOKINETICS DRUG DELIVERY SYSTEM CARDIOTOXICITY

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 21442-01-3D (N-(2-HYDROXYPROPYL)-METHACRYLAMIDE)
25316-40-9 (ADRIAMYCIN)
23214-92-8Q (ADRIAMYCIN)

L7 ANSWER 12 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1988:267388 BIOSIS
DOCUMENT NUMBER: PREV198886006632; BA86:6632
TITLE: ANTICANCER AGENTS COUPLED TO N-2 HYDROXYPROPYLMETHACRYLAMIDE COPOLYMERS II. EVALUATION OF DAUNOMYCIN CONJUGATES IN-VIVO AGAINST L1210 LEUKEMIA.
AUTHOR(S): DUNCAN R [Reprint author]; KOPECKOVA P; STROHALM J; HUME I C; LLOYD J B; KOPECEK J
CORPORATE SOURCE: DEP BIOLOGICAL SCI, UNIV KEELE, KEELE, STAFFORDSHIRE ST5 5BG, UK
SOURCE: British Journal of Cancer, (1988) Vol. 57, No. 2, pp. 147-156.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 2 Jun 1988
Last Updated on STN: 2 Jun 1988

TI ANTICANCER AGENTS COUPLED TO N-2 HYDROXYPROPYLMETHACRYLAMIDE COPOLYMERS II. EVALUATION OF DAUNOMYCIN CONJUGATES IN-VIVO AGAINST L1210 LEUKEMIA.

AB DBA2 mice were inoculated i.p. with 105L1210 cells. Animals subsequently treated with daunomycin (single i.p. dose, 0.25-5.0 mg kg-1) all died. The maximum increase in mean survival time observed was .apprx. 135%. Animals treated with N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers conjugated to daunomycin (DNM) showed a significant increase in mean survival time when the **polymerdrug linkage** was **biodegradable** (i.e., Gly-Phe-Leu-Gly). Such treatment also produced a number of long term survivors (> 50 days). In contrast, HPMA copolymer conjugated to DNM via a non-degradable linkage (Gly-Gly) produced no increase in survival time relative to untreated control animals. The effect observed with **biodegradable** HPMA copolymer-DNM conjugates was dependent on the concentration of conjugated drug administered (optimum > 5 mg kg-1); the frequency of administration (multiple doses were more effective than single); the timing of administration (single doses given on days 1 and 3 were most effective); and the site of tumor inoculation and route of drug administration. **Biodegradable** HPMA copolymer-DNM conjugates administered i.p. were active against L1210 inoculated s.c. at higher doses than required to curb a peritoneal tumor. Under certain experimental conditions polymer-DNM conjugates containing fucosylamine or galactosamine proved more active than conjugates without the carbohydrate moiety. The mechanism of drug-conjugate action in vivo is at present unclear. Radioiodination of polymer showed .apprx. 75% of polymerdrug conjugate to be excreted 24 h after i.p. administration. Synthesis of HPMA conjugates containing [3H]DNM showed that polymer containing Gly-Gly-[3H]DNM was excreted (60% of radioactivity in the urine, 24 h) in macromolecular form. In contrast polymer containing Gly-Phe-Leu-Gly-[3H]DNM was largely excreted in the form of low molecular weight species.

CC Cytology - Animal 02506
Biochemistry studies - General 10060

Pathology - Therapy 12512
Metabolism - General metabolism and metabolic pathways 13002
Blood - Blood, lymphatic and reticuloendothelial pathologies 15006
Blood - Lymphatic tissue and reticuloendothelial system 15008
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Clinical pharmacology 22005
Neoplasms - Pathology, clinical aspects and systemic effects 24004
Neoplasms - Neoplastic cell lines 24005
Neoplasms - Therapeutic agents and therapy 24008
Neoplasms - Blood and reticuloendothelial neoplasms 24010
Laboratory animals - General 28002
Tissue culture, apparatus, methods and media 32500

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Metabolism; Pharmacology; Tumor Biology

IT Miscellaneous Descriptors
MURINE LEUKEMIA L1210 CELLS ANTINEOPLASTIC-DRUG PHARMACEUTICAL ADJUNCT-DRUG PHARMACODYNAMICS PHARMACOKINETICS DRUG CARRIER TUMOR-SPECIFIC DRUG-TARGETING MEAN SURVIVAL TIME ANIMAL MODEL

ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates

RN 21442-01-3D (N-(2-HYDROXYPROPYL)METHACRYLAMIDE)
20830-81-3 (DAUNOMYCIN)

L7 ANSWER 13 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1987:466304 BIOSIS
DOCUMENT NUMBER: PREV198784111744; BA84:111744
TITLE: COUPLING OF NALTREXONE TO **BIODEGRADABLE** POLY-ALPHA-AMINO ACIDS.
AUTHOR(S): NEGISHI N [Reprint author]; BENNETT D B; SHO C-S; JEONG S Y; VAN HEESWIJK W A R; FEIJEN J; KIM S W
CORPORATE SOURCE: DEP PHARM, UNIV UTAH, SALT LAKE CITY, UTAH 84112, USA
SOURCE: Pharmaceutical Research (New York), (1987) Vol. 4, No. 4, pp. 305-310.
CODEN: PHREEB. ISSN: 0724-8741.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 7 Nov 1987
Last Updated on STN: 7 Nov 1987

TI COUPLING OF NALTREXONE TO **BIODEGRADABLE** POLY-ALPHA-AMINO ACIDS.

AB The narcotic antagonist naltrexone (I) was modified at the 3 and 14 hydroxyl positions and covalently coupled to a **biodegradable** poly(α-amino acid) backbone through a labile bond. Selective acetylation of I with acetic anhydride gave naltrexone-3-acetate (II), which was subsequently succinoylated to naltrexone-3-acetate-14-hemisuccinate (III) with succinic anhydride. The polymeric backbone chosen for initial coupling experiments was poly-N5-(3-hydroxypropyl)-L-glutamine (PHPG). The side-chain hydroxyl functionality permitted covalent bonding of III through an ester linkage. Hydrolysis of covalently bound drug to give naltrexone or its derivatives (II and III) should be much slower than diffusion of drug through the polymer matrix. While hydrolysis of naltrexone from the polymer side chain is first order, release of drug from the matrix can be zero order due to the geometry of the device and the physical and chemical interactions between naltrexone and the polymer matrix. In vitro studies of PHPG-naltrexone conjugate in disk form did not show constant release because of the hydrophilic nature of the polymer backbone and the changing local chemical environment upon

hydrolysis of drug-**polymer linkages**. The conjugated system was made more hydrophobic by coupling drug to copolymers of hydroxypropyl-L-glutamine (HPG) and L-leucine. Conjugates of III coupled with copoly(HPG-70/Leu-30) demonstrated a nearly constant, but slightly declining release rate of naltrexone and its derivatives for 28 days in vitro.

CC Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Pharmacology - Drug metabolism and metabolic stimulators 22003
Pharmacology - Neuropharmacology 22024

IT Major Concepts
Pharmacology

IT Miscellaneous Descriptors
NARCOTIC ANTAGONIST DRUG DELIVERY SYSTEM

RN 16590-41-3 (NALTREXONE)

L7 ANSWER 14 OF 16 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 1986:163833 BIOSIS
DOCUMENT NUMBER: PREV198681074249; BA81:74249
TITLE: POLY-L-ASPARTIC-ACID AS A CARRIER FOR DOXORUBICIN A COMPARATIVE IN-VIVO STUDY OF FREE AND POLYMER-BOUND DRUG.
AUTHOR(S): PRATESI G [Reprint author]; SAVI G; PEZZONI G; BELLINI O; PENCO S; TINELLI S; ZUNINO F
CORPORATE SOURCE: IST NA STUDIO CURA TUMORI, MILAN
SOURCE: British Journal of Cancer, (1985) Vol. 52, No. 6, pp. 841-848.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH
ENTRY DATE: Entered STN: 26 Apr 1986
Last Updated on STN: 26 Apr 1986

TI POLY-L-ASPARTIC-ACID AS A CARRIER FOR DOXORUBICIN A COMPARATIVE IN-VIVO STUDY OF FREE AND POLYMER-BOUND DRUG.

AB The synthetic polypeptide, poly-L-aspartic acid (PAA, mol. wt=20,000) has been used as a macromolecular carrier for doxorubicin. The drug may be released in vivo through hydrolysis of the ester linkage formed between the carboxyl groups of the polymer and the drug side chain. PAA has been found to be a suitable carrier since it is a soluble, **biodegradable**, multivalent and nontoxic polymer. The toxicity and the therapeutic efficacy of free and **polymer-linked** doxorubicin have been evaluated in normal and tumour-bearing mice, using a varity of experimental tumour systems. In studies on single and multiple drug administration, the results indicated that the polymeric derivative of doxorubician had approximately 3-fold lower toxicity than did free drug. In addition, the severity of specific toxin effects, including cardio- and vesicant toxicity, were appreciably reduced followig conjugation to PAA. The doxorubidin-PAA conjugate gave similar or rather greater therapeutic effects than free drug at less toxic doses. This effect, more evident in the highly sensitive tumours, suggest an improvement of the therapeutic index of the **polymer-linked** drug.

CC Cytology - Animal 02506
Biochemistry studies - General 10060
Biochemistry studies - Proteins, peptides and amino acids 10064
Pathology - Therapy 12512
Cardiovascular system - Heart pathology 14506
Cardiovascular system - Blood vessel pathology 14508
Pharmacology - Drug metabolism and metabolic stimulators 22003
Toxicology - Pharmacology 22504
Neoplasms - Therapeutic agents and therapy 24008

IT Major Concepts
Cardiovascular System (Transport and Circulation); Pharmacology;

Toxicology; Tumor Biology
IT Miscellaneous Descriptors
MICE ANTINEOPLASTIC-DRUG PHARMACOTOXICITY CARDIOTOXICITY VESICANT TOXICITY THERAPEUTIC INDEX
ORGN Classifier
Muridae 86375
Super Taxa
Rodentia; Mammalia; Vertebrata; Chordata; Animalia
Taxa Notes
Animals, Chordates, Mammals, Nonhuman Vertebrates, Nonhuman Mammals, Rodents, Vertebrates
RN 25608-40-6Q (POLY-L-ASPARTIC-ACID)
26063-13-8Q (POLY-L-ASPARTIC-ACID)
23214-92-8 (DOXORUBICIN)

L7 ANSWER 15 OF 16 MEDLINE on STN
ACCESSION NUMBER: 89240328 MEDLINE
DOCUMENT NUMBER: PubMed ID: 3508536
TITLE: Coupling of naltrexone to **biodegradable** poly(alpha-amino acids).
AUTHOR: Negishi N; Bennett D B; Cho C S; Jeong S Y; Van Heeswijk W A; Feijen J; Kim S W
CORPORATE SOURCE: Department of Pharmaceutics, University of Utah, Salt Lake City 84112.
CONTRACT NUMBER: DA 02391 (NIDA)
SOURCE: Pharmaceutical research, (1987 Aug) 4 (4) 305-10. Journal code: 8406521. ISSN: 0724-8741.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198906
ENTRY DATE: Entered STN: 19900306
Last Updated on STN: 19970203
Entered Medline: 19890612
TI Coupling of naltrexone to **biodegradable** poly(alpha-amino acids).
AB The narcotic antagonist naltrexone (I) was modified at the 3 and 14 hydroxyl positions and covalently coupled to a **biodegradable** poly(alpha-amino acid) backbone through a labile bond. Selective acetylation of I with acetic anhydride gave naltrexone-3-acetate (II), which was subsequently succinoylated to naltrexone-3-acetate-14-hemisuccinate (III) with succinic anhydride. The polymeric backbone chosen for initial coupling experiments was poly-N5-(3-hydroxypropyl)-L-glutamine (PHPG). The side-chain hydroxyl functionality permitted covalent bonding of III through an ester linkage. Hydrolysis of covalently bound drug to give naltrexone or its derivatives (II and III) should be much slower than diffusion of drug through the polymer matrix. While hydrolysis of naltrexone from the polymer side chain is first order, release of drug from the matrix can be zero order due to the geometry of the device and the physical and chemical interactions between naltrexone and the polymer matrix. In vitro studies of PHPG-naltrexone conjugate in disk form did not show constant release because of the hydrophilic nature of the polymer backbone and the changing local chemical environment upon hydrolysis of drug-**polymer linkages**. The conjugated system was made more hydrophobic by coupling drug to copolymers of hydroxypropyl-L-glutamine (HPG) and L-leucine. Conjugates of III coupled with copoly(HPG-70/Leu-30) demonstrated a nearly constant, but slightly declining release rate of naltrexone and its derivatives for 28 days in vitro.
CT Check Tags: Support, U.S. Gov't, P.H.S.
*Amino Acids: ME, metabolism
Drug Carriers
Esters

*Naltrexone: ME, metabolism
Spectrophotometry, Infrared
RN 16590-41-3 (Naltrexone)
CN 0 (Amino Acids); 0 (Drug Carriers); 0 (Esters)

L7 ANSWER 16 OF 16 MEDLINE on STN
ACCESSION NUMBER: 86077544 MEDLINE
DOCUMENT NUMBER: PubMed ID: 4074638
TITLE: Poly-L-aspartic acid as a carrier for doxorubicin: a comparative in vivo study of free and polymer-bound drug.
AUTHOR: Pratesi G; Savi G; Pezzoni G; Bellini O; Penco S; Tinelli S; Zunino F
SOURCE: British journal of cancer, (1985 Dec) 52 (6) 841-8. Journal code: 0370635. ISSN: 0007-0920.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198602
ENTRY DATE: Entered STN: 19900321
Last Updated on STN: 19900321
Entered Medline: 19860211

TI Poly-L-aspartic acid as a carrier for doxorubicin: a comparative in vivo study of free and polymer-bound drug.

AB The synthetic polypeptide, poly-L-aspartic acid (PAA, mol. wt = 20,000) has been used as a macromolecular carrier for doxorubicin. The drug may be released in vivo through hydrolysis of the ester linkage formed between the carboxyl groups of the polymer and the drug side chain. PAA has been found to be a suitable carrier since it is a soluble, **biodegradable**, multivalent and nontoxic polymer. The toxicity and the therapeutic efficacy of free and **polymer-linked** doxorubicin have been evaluated in normal and tumour-bearing mice, using a variety of experimental tumour systems. In studies on single and multiple drug administration, the results indicated that the polymeric derivative of doxorubicin had approximately 3-fold lower toxicity than did free drug. In addition, the severity of specific toxic effects, including cardio- and vesicant toxicity, were appreciably reduced following conjugation to PAA. The doxorubicin-PAA conjugate gave similar or rather greater therapeutic effects than free drug at less toxic doses. This effect, more evident in the highly sensitive tumours, suggests an improvement of the therapeutic index of the **polymer-linked** drug.

CT Check Tags: Comparative Study; Female; Male; Support, Non-U.S. Gov't
Animals
Dose-Response Relationship, Drug
*Doxorubicin: AD, administration & dosage
Doxorubicin: TU, therapeutic use
Doxorubicin: TO, toxicity
Heart: DE, drug effects
Lung Neoplasms: DT, drug therapy
Mammary Neoplasms, Experimental: DT, drug therapy
Mice
Mice, Inbred BALB C
Mice, Inbred C3H
Mice, Inbred C57BL
*Peptides
Rats
Vehicles
RN 23214-92-8 (Doxorubicin); 26063-13-8 (polyaspartate)
CN 0 (Peptides); 0 (Vehicles)

=> DIS HIST

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     (FILE 'HOME' ENTERED AT 09:09:04 ON 23 JUL 2004)

     FILE 'CAPLUS' ENTERED AT 09:10:15 ON 23 JUL 2004
               E "391612-50-3"/BI,RN 25
L1             1 S E3

     INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DISSABS,
     DDFB, DDFU, DGENE, DRUGB, DRUGMONOG2, ...' ENTERED AT 09:13:17 ON 23 JUL
     2004
                SEA L1
               ---------
               1    FILE CAPLUS
               1    FILE TOXCENTER
L2              QUE L1
               ---------

     FILE 'CAPLUS, TOXCENTER' ENTERED AT 09:14:17 ON 23 JUL 2004
L3             2 S L1

     FILE 'CAPLUS, BIOSIS, MEDLINE' ENTERED AT 09:15:57 ON 23 JUL 2004
L4            19 S POLYMER? LINK? AND BIODEGRAD?
L5             3 S L4 AND (GREENWALD,R? OR ZHAO,H?)/AU
L6             2 DUP REM L5 (1 DUPLICATE REMOVED)
L7            16 S L4 NOT L5

=>

---Logging off of STN---


=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                57.84      74.79

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
                                                   ENTRY    SESSION
CA SUBSCRIBER PRICE                                -7.35      -8.83

STN INTERNATIONAL LOGOFF AT 09:18:47 ON 23 JUL 2004
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L Number	Hits	Search Text	DB	Time stamp
-	0	WO-98-47496-$.did.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/23 08:41
-	540	Duncan-R$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:08
-	6	Duncan-R$.in. AND Ferruti-P$.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:08
-	756	camptothecin.ti.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:08
-	256	514/283.ccls. AND camptothecin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/23 09:27
-	43	514/279.ccls. AND camptothecin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:08
-	0	"polymeric prodrug conjugate"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:08
-	131	prodrug NEAR conjugate	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:08
-	44	prodrug NEAR conjugate AND polymeric	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:08
-	18	camptothecin.ti. AND polymer.ab.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:09
-	6	424/78.18.ccls. AND camptothecin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:09
-	0	greenwald-richard.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:09
-	527	enzon	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:09
-	100	(camptothecin AND derivative).ti.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:09
-	0	(camptothecin AND derivative).ti. AND "20-O"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:11

-	64	"20-O"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/21 19:11
-	42	zhao-hong.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/23 08:41
-	21	530/322.ccls. AND camptothecin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/23 09:29
-	1	530/322.ccls. AND camptothecin AND polymer ADJ conjugate	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/23 09:30
-	7	525/54.1.ccls. AND camptothecin AND polymer ADJ conjugate	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/23 09:37
-	5	"6251382"	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/07/23 09:37